

/Amy Bowman/

CONSIDERED: /AB/

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Curriculum Vitae

RICHARD S. GEARY, Ph. D.

EDUCATION:

Ph.D., Pharmaceutics, University of Texas at Austin, 1988

B.S., Biology, Texas A&M University, 1980

PROFESSIONAL POSITIONS AND EXPERIENCE:

2008-Present	Senior Vice President of Development, Isis Pharmaceuticals <i>Job Description:</i> Responsible for preclinical and clinical development of antisense drugs.
2003-2008	Vice President of Pharmacokinetics and Metabolism, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics <i>Job Description:</i> Provide direction and support for preclinical and clinical development of oligonucleotide therapeutics.
2001-2003	Executive Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics
1998-2001	Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics
1997-1998	Associate Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics
1995-1997	Assistant Director of Pharmacokinetics, Isis Pharmaceuticals, Department of Toxicology and Pharmacokinetics
1993-1995	Manager, Southwest Research Institute, Applied Biopharmaceutics and Physical Chemistry, Department of Applied Chemistry and Chemical Engineering
1992-1993	Group Leader, Southwest Research Institute, Pharmaceutics and Pharmacology Section, Department of Applied Chemistry and Chemical Engineering
1990-1992	Senior Research Scientist, Southwest Research Institute, Pharmaceutics and Pharmacology Section, Department of Applied Chemistry and Chemical Engineering

1987-1990 Research Scientist, Southwest Research Institute, Pharmaceuticals and
Pharmacology Section, Department of Applied Chemistry and Chemical
Engineering

CONTINUING EDUCATION COURSES:

Incorporation of Pharmacokinetic and Pharmacodynamic Data into Risk Assessment, Nashville, TN, SOT, 2002

Prediction of Human Toxicity and Metabolic Fate of Drugs Using In Vitro Systems, San Francisco, CA, SOT, 2001

Advances in Non-Invasive Micrometer and Nanometer Scale Cellular/Tissue Vital Imaging, Philadelphia, PA, SOT, 2000

Toxicokinetics and Physiologically-Based Toxicokinetics in Toxicology and Risk Assessment, Philadelphia, PA, SOT, 2000

Advanced Topics in Toxicokinetics, Anaheim, CA, SOT, 1996

New Approaches for Studying Cytochrome P450-Dependant Toxicant Metabolism, Anaheim, CA, SOT, 1996

Application of Pharmacokinetics to Toxicological Testing, Dallas, TX, SOT, 1994

Implementing PBPK Models, Dallas, TX, SOT, 1991

Introduction to Physiologically-based Pharmacokinetic Modeling, Dallas, TX, SOT, 1991

TRAINING COURSES:

Understanding GLP's (Video), 1998

Short Course in Population Pharmacokinetics Data Analysis using the NONMEM System, April 20-22, 1998

Performance Management and Appraisal Training Program – The Coach Approach, 1997

Population Pharmacokinetics and P-Pharm Workshop, April 1-3, 1996

GLP Training – SwRI 1992-1995

Total Quality Management – SwRI 1993

One-week Workshop on Advanced Methods in Pharmacokinetics/Pharmacodynamics, April 1-6, 1990

BOOKS AND CHAPTERS:

Bennett, C. F., Swayze, E., Geary, R., Henry, S., Tillman, L., Hardee, G. (2008) Antisense Oligonucleotide-based Therapeutics. *Gene and Cell Therapy: Mechanisms and Strategies*. 497-522

Yu, R. Z., Geary, R. S., and Levin, A. A. (2007). Pharmacokinetics and Pharmacodynamics of Antisense Oligonucleotides. In *Encyclopedia of Molecular Cell biology and Molecular Medicine* (R. A. Meyers, ed. Wiley-VCH, Weinheim, Germany.

Geary, R. S., Yu, R. Z., Siwkowski, A., and Levin, A. A. (2007). Pharmacokinetic/Pharmacodynamic Properties of Phosphorothioate 2' - O-(2-Methoxyethyl)-Modified Antisense Oligonucleotides in Animals and Man. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 305-326. Taylor & Francis Group, Boca Raton, FL.

Hardee, G. E., Tillman, L. G., and Geary, R. S. (2007). Routes and Formulations for Delivery of Antisense Oligonucleotides. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 217-236. Taylor & Francis Group, Boca Raton, FL.

Levin, A. A., Yu, R. Z., and Geary, R. S. (2007). Basic Principles of the Pharmacokinetics of Antisense Oligonucleotide Drugs. In *Antisense Drug Technology, Principles, strategies and applications*. S. T. Crooke, ed., Vol. 2, pp. 183-215. Taylor & Francis Group, Boca Raton, FL.

Yu, R., Geary, R.S., Watanabe, T., Levin, A.A., Schoenfeld, L.S., Pharmacokinetic properties in humans. *Antisense Drug Technology: Principles, Strategies, and Applications*. (2001) Marcel Dekker, Inc. 183-200.

Geary, R.S., Yu, R., Leeds, J.M., Watanabe, T., Henry, S.P., Levin, A.A., Templin, M.V. Pharmacokinetic properties in animals. *Antisense Drug Technology. Principles, Strategies, and Applications*. (2001) Marcel Dekker, Inc. 119-154.

Bennett, F.C., Butler, M., Cook, D.P., Geary, R.S., Levin, A.A., Mehta, R., Teng, C.L., Deshmukh, H., Tillman, L., Hardee, G. (2000) Antisense oligonucleotide-based therapeutics. *Gene Therapy*. Marcel Dekker, Inc. 305-332.

Levin, A.A., Geary, R.S., Leeds, J.M., Monteith, D.K., Yu, R., Templin, M.V. and Henry, S.P., (1998). The pharmacokinetics and toxicity of phosphorothioate oligonucleotides. *Biotechnology and Safety Assessment*, Taylor & Francis. 1: 151-175.

Levin, A.A., Monteith, D.K., Leeds, J.M., Nicklin, P.L., Geary, R.S., Butler, M., Templin, M.V. and Henry, S.P., (1998). Toxicity of oligodeoxynucleotide therapeutic agents. *Antisense Research and Application*. Crooke, S.T. Heidelberg, Springer. 131: 169-215.

Leeds, J.M. and Geary, R.S., (1998). Pharmacokinetic properties of phosphorothioate oligonucleotides in humans. *Antisense Research and Application*. Crooke, S.T. Heidelberg, Springer. 131: 217-232.

Geary, R.S., (1993). Drug delivery systems and recombinant proteins. *Biotechnology and Safety Assessment*, Raven, New York, NY.

PROFESSIONAL PUBLICATIONS:

Geary RS. (2009) Antisense Oligonucleotide Pharmacokinetics and Metabolism. *Expert Opinion, Drug Metabolism & Toxicology*. 2009 Apr;5(4):381-91.

Geary RS, Wancewicz E, Matson J, Pearce M, Siwkowski A, Swayze E, Bennett F. (2009) Effect of Dose and Plasma Concentration on Liver Uptake and Pharmacologic Activity of a 2'-Methoxyethyl Modified Chimeric Antisense Oligonucleotide Targeting PTEN. *Biochemical Pharmacology*. 2009 Apr 21 published online. Currently in press.

Yu R.Z., Lemonidis K.M., Graham M.J., Matson J.E., Crooke R.M., Tribble D.L., Wedel M.K., Levin A.A., Geary R.S. (2009) Cross-species comparison of In Vivo PK/PD relationships for second generation antisense oligonucleotides targeting apolipoprotein B-100. *Biochemical Pharmacology*. 2009 March, 77 (5) 910-919.

Yu R.Z., Geary R.S., Flaim J., Riley G., Tribble D., van Vliet A., Wedel M. (2009) Lack of Pharmacokinetic Interaction of Mipomersen Sodium (ISIS 301012), a 2'-O-Methoxyethyl Modified Antisense Oligonucleotide Targeting Apolipoprotein B-100 Messenger RNA, with Simvastatin and Ezetimibe. *Clinical Pharmacokinetics*. 2009; 48 (1): 39-50.

Crosby J.R., Guha M., Tung D., Miller D.A., Bender B., Condon T.P., York-Defalco C., Geary R.S., Monia B.P., Karras J.G., Gregory S.A. (2007). Inhaled CD86 Antisense Oligonucleotide Suppresses Pulmonary Inflammation and Airway Hyper-responsiveness in Allergic Mice. *J Pharm Sci*. 2008 Jan; 97 (1): 225-36.

Tillman L.G., Geary R.S., and Hardee G.E. (2007). Oral Delivery of Antisense Oligonucleotides In Man. *J Pharm Sci*. 2008 Jan; 97 (1): 225-36.

Yu R.Z., Kim T.W., Hong A., Watanabe T.A., Gaus H.J., and Geary R.S. (2007). Cross-Species Pharmacokinetic Comparison from Mouse to Man of a Second Generation Antisense Oligonucleotide ISIS 301012, Targeting Human ApoB-100. *Drug Metab. Dispos.* 35, 460-468.

Karras J.G., Crosby J.R., Guha M., Tung D., Miller D.A., Gaarde W.A., Geary R.S., Monia B.P., and Gregory S.A. (2007). Anti-inflammatory activity of inhaled IL-4 receptor-alpha antisense oligonucleotide in mice. *Am J Respir Cell Mol Biol* 36, 276-85.

Geary R.S., Bradley J.D., Watanabe T., Kwon Y., Wedel M., van Lier J.J., vanVliet A.A. (2006). Lack of Pharmacokinetic Interaction for ISIS 113715, a 2'-O-Methoxyethyl Modified Antisense Oligonucleotide Targeting Protein Tyrosine Phosphatase 1B Messenger RNA, with Oral Antidiabetic Compounds Metformin, Glipizide or Rosiglitazone. *Clinical Pharmacokinetics*: Volume 45(8)2006pp 789-801.

Miner P.B., Jr., Geary R.S., Matson J., Chuang E., Xia S., Baker B.F., and Wedel M.K. (2006). Bioavailability and therapeutic activity of alicaforsen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. *Aliment Pharmacol Ther* 23, 1427-1434.

Watanabe, T.A., Geary, R.S., and Levin, A.A. (2006). Plasma Protein Binding of an Antisense Oligonucleotide Targeting Human ICAM-1 (ISIS 2302). *Oligonucleotides* 16, 169-180.

Soucy, N.V., Riley J.P., Templin, M.V., Geary, R.S., de Peyster, A., and Levin, A.A. (2006). Maternal and fetal distribution of a phosphorothioate oligonucleotide in rats after intravenous infusion. *Birth Defects Res B Dev Reprod Toxicol* 77 (1):22-28.

Chen, W., Langer, R.M., Janczewska, S., Furian, L., Geary, R., Qu, X., Wang, M., Verani, R., Condon, T., Stecker, K., Bennett, C. F., and Stepkowski, S. M., (2005) Methoxyethyl-modified intercellular adhesion molecule-1 antisense phosphorothioateoligonucleotides inhibit allograft rejection, ischemic-reperfusion injury, and cyclosporine-induced nephrotoxicity, *Transplantation* 79 (4): 401-408.

Advani, R., Lum, B.L., Fisher, G.A., Halsey, J., Geary, R.S., Holmlund, J.T., Kwoh, T.J., Dorr, F.A., & Sikic, B.I. (2005) A phase I trial of aprinocarsen (ISIS 3521/LY900003), an antisense inhibitor of protein kinase C- α administered as a 24-hour weekly infusion schedule in patients with advanced cancer. *Invest New Drugs*, 23, 467-477.

Albertshofer, K., Siwkowski, A.M., Wancewicz, E.V., Esau, C.C., Watanabe, T., Nishihara, K.C., Kinberger, G.A., Malik, L., Eldrup, A.B., Manoharan, M., Geary, R.S., Monia, B.P., Swayze, E.E., Griffey, R.H., Bennett, C.F. and A., M.M. (2005). "Structure-Activity Relationship Study on a Simple Cationic Peptide Motif for Cellular Delivery of Antisense Peptide Nucleic Acid." *J Med Chem*. 2005 Oct 20;48(21):6741-9.

Murphy, A.T., Brown-Augsburger, P., Yu, R.Z., Geary, R.S., Thibodeaux, S. and Ackermann, B.L. (2005). Development of an ion-pair reverse-phase liquid chromatographic/tandem mass spectrometry method for the determination of an 18-mer phosphorothioate oligonucleotide in mouse liver tissue. *Eur J Mass Spectrom (Chichester, Eng)* 11(2): 209-215.

Villalona-Calero, M.A., Ritch, P., Figueroa, J.A., Otterson, G.A., Belt, R., Dow, E., George, S., Leonardo, J., McCachren, S., Miller, G.L., Modiano, M., Valdivieso, M., Geary, R.S., Oliver, J.W. and Holmlund, J. (2004). A phase I/II study of LY900003, an Antisense inhibitor of protein kinase C- α , in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer. *Clin. Cancer Res*. 10(18 Pt 1): 6086-6093.

Yu, R.Z., Geary, R.S. and Levin, A.A. (2004). Application of novel quantitative bioanalytical methods for pharmacokinetic and pharmacokinetic/pharmacodynamic assessments of antisense oligonucleotides. *Curr Opin Drug Discov Devel* 7(2): 195-203.

Yu, R.Z., Geary, R.S., Monteith, D.K., Matson, J., Truong, L., Fitchett, J. and Levin, A.A. (2004). Tissue disposition of a 2'-O-(2-methoxy) ethyl modified antisense oligonucleotides in monkeys. *J. Pharm. Sci.* 93: 48-59.

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Yu, R. Z., Su, J. Q., Grundy, J. S., Geary, R. S., Sewell, K. L., Dorr, A., and Levin, A. A. (2003). Prediction of clinical responses in a simulated phase III trial of Crohn's patients administered the antisense phosphorothioate oligonucleotide ISIS 2302: comparison of proposed dosing regimens. *Antisense and Nucleic Acid Drug Development* 13, 57-66.

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Yu R.Z., Baker B., Chappell A., Geary R.S., Chueng E., Levin A.A. Development of an ultrasensitive noncompetitive hybridization-ligation enzyme-linked immunosorbent assay for the determination of phosphorothioate oligodeoxynucleotide in plasma. *Anal Biochem.* 304:19-25, 2002.

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Henry, S.P., Geary, R.S., Yu, R., and Levin, A.A. Drug Properties of Second-Generation Antisense Oligonucleotides: How do They Measure Up to Their Predecessors. *Cur. Opin. Invest. Drugs.* 2(10):1444-1449, 2001.

Geary, R. S., Yu, R.Z., Levin, A.A. Pharmacokinetics of phosphorothioate antisense oligodeoxynucleotides. *Current Opinion in Investigational Drugs.* 2(4) :562-573, 2001.

Geary, R. S., Watanabe, T. A., Truong, L., Freier, S., Lesnik, E. A., Sioufi, N. B., Sasmor, H., Manoharan, M., and Levin, A. A. Pharmacokinetic properties of 2'-O-(2-methoxyethyl)-modified oligonucleotide analogs in rats. *J Pharmacol Exp Ther* 296(3):890-897, 2001.

Geary, R. S., Khatsenko, O., Bunker, K., Crooke, R., Moore, M., Burckin, T., Truong, L., Sasmor, H., and Levin, A. A. Absolute bioavailability of 2'-O-(2-methoxyethyl)-modified antisense oligonucleotides following intraduodenal instillation in rats. *J Pharmacol Exp Ther* 296(3):898-904, 2001.

Yu, R., Geary, R., Leeds, J., Watanabe, T., Moore, M., Fitchett, J., Matson, J., Burckin, T., Templin, M., and Levin, A. Comparison of pharmacokinetics and tissue disposition of an antisense phosphorothioate oligonucleotide targeting human Ha-ras mRNA in mouse and monkey. *J Pharm Sci* 90(2):182-193, 2001.

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Cunningham, C. C., Holmlund, J. T., Schiller, J. H., Geary, R. S., Kwoh, T. J., Dorr, A., and Nemunaitis, J. A phase I trial of c-ras kinase antisense oligonucleotide isis 5132 administered as a continuous intravenous infusion in patients with advanced cancer. *Clin Cancer Res* 6(5):1626-1631, 2000.

Leeds, J. M., Henry, S. P., Geary, R., Burckin, T., and Levin, A. A. Comparison of the pharmacokinetics of subcutaneous and intravenous administration of a phosphorothioate oligodeoxynucleotide in cynomolgus monkeys. *Antisense Nucleic Acid Drug Dev* 10(6):435-441, 2000.

Templin, M. V., Levin, A. A., Graham, M. J., Aberg, P. M., Axelsson, B. I., Butler, M., Geary, R. S., and Bennett, C. F. Pharmacokinetic and toxicity profile of a phosphorothioate oligonucleotide following inhalation delivery to lung in mice. *Antisense Nucleic Acid Drug Dev* 10(5):359-368, 2000.

Yuen, A. R., Halsey, J., Fisher, G. A., Holmlund, J. T., Geary, R. S., Kwoh, T. J., Dorr, A., and Sikic, B. I. Phase I study of an antisense oligonucleotide to protein kinase C- α . (ISIS 3521/CGP 64128A) in patients with cancer. *Clin. Cancer Res.* 5(11):3357-3363, 1999.

Nemunaitis, J., Holmlund, J. T., Kraynak, M., Richards, D., Bruce, J., Ognoskie, N., Kwoh, T. J., Geary, R., Dorr, A., Von Hoff, D., and Eckhardt, S. G. Phase I evaluation of ISIS 3521, an antisense oligodeoxynucleotide to protein kinase C- α , in patients with advanced cancer. *J. Clin. Oncol.* 17(11):3586-3595, 1999.

Geary, R.S., Matson, J., and Levin, A.A. A Nonradioisotope Biomedical Assay for Intact Oligonucleotide and Its Chain-Shortened Metabolites Used for Determination of Exposure and Elimination Half-Life of Antisense Drugs in Tissue. *Anal. Biochem.* 274: 241-248, 1999.

Yu, R.Z., Geary, R.S., Leeds, J.M., Watanabe, T., Fitchett, J.R., Matson, J.E., Mehta, R., Hardee, G.R., Templin, M.V., Huang, K., Newman, M.S., Quinn, Y., Uster, P., Zhu, G., Working, P.K., Horner, M., Nelson, J., and Levin, A.A. Pharmacokinetics and tissue disposition in monkeys of an antisense oligonucleotide inhibitor of Ha-Ras encapsulated in stealth liposomes. *Pharm. Res.* 16 (8): 1309-1315, 1999.

Monteith, D.K., Horner, M.J., Gillett, N.A., Butler, M., Geary, R., Burckin, T., Ushiro-Watanabe, T., and Levin, A. Evaluation of the renal effects of an antisense phosphorothioate oligodeoxynucleotide in monkeys. *Toxicologic Pathology.* 27 (3): 307-317, 1999.

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ABSTRACTS AND PRESENTATIONS:

M.R. Hodges, MB BS, BSc, E. Castelleo, MD, A. Chen, MA, R.S. Geary, PhD, J.G. Karras, PhD, D. Shapiro, MB BS, B. Yeung, BSc, R. Yu, PhD, S.A. Gregory, PhD. Randomized, Double-Blind, Placebo Controlled First in Human Study of Inhaled AIR645, an IL-4R Oligonucleotide, in Healthy Volunteers. Presented at ATS, San Diego, CA, May 18, 2009. Published 4/24/09 on ATS website.

Fey RA¹, Geary RS¹, Norris DA¹, Boyd RB² and Henry SP¹. 1: Isis Pharmaceuticals, Inc. 2: Northern Biomedical Research. Pharmacokinetics of an Antisense Oligonucleotide Administered as a Continuous Intrathecal Infusion in Monkey. Presented at 58th Annual SOT Meeting and ToxExpo, Baltimore Convention Center, Baltimore, MD. March 15-18, 2009.

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Baek MS, Yu R, Gaus H and Geary RS. In vitro metabolism of Mipomersen (ISIS 301012), a second-generation antisense oligonucleotide targeting human apoB-100. Presented at AAPS Annual Meeting, Atlanta, GA, November 16-20, 2008.

Geary, RS. Pharmacokinetics of Antisense Oligonucleotides: Relationship to Safety and Pharmacology. Oral presentation at American College of Toxicology Annual Meeting, Tucson, AZ, November 9-12, 2008.

Geary, RS. Pioneering RNA-based Drug Discovery & Development. Oral presentation at BIOCOM Investor Conference, La Jolla, CA, October 28, 2008.

Geary, RS. Bioanalytical Issues and Applications for Antisense Oligonucleotide Development: From Bench to Bedside. Oral presentation at DIA, Washington DC, September 22-24, 2008.

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Geary RS, Pearce M, Wancewicz E, Hung G, Henry SP, Matson J, Crosby J, Karras J, Gregory S, and Yu RZ. Pharmacokinetic and Pharmacodynamic Effects of 2'-MOE Partially Modified Phosphorothioate Antisense Oligonucleotides Administered Directly to Lung and Cerebrospinal Fluid. Presented at Society of Toxicology 47th Annual Meeting & ToxExpo, Seattle, WA, March 16-20, 2008.

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PROFESSIONAL MEMBERSHIPS:

- 1) Society of Toxicology (SOT)
- 2) American Association of Pharmaceuticals Scientists (AAPS)
- 3) American Society for Clinical Pharmacology & Therapeutics (ASCPT)
- 4) Rho Chi Honor Society